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TITLE: A Population-Based Randomized Trial to Assess the Effects of Short-Term Cessation of HRT on Mammography Assessments and Breast Density

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ABSTRACT

This randomized controlled trial is designed to test whether short-term (1-2 months) HRT cessation will sufficiently lower breast density to decrease the proportion of women who receive a recommendation for additional evaluation following a screening mammogram, and to examine whether there is a trend by duration of HRT cessation. The study is being conducted at Group Health Cooperative, a managed health care organization with an organized breast cancer screening program. We are projecting that we will recruit between 630-785 women to randomize to one of three HRT arms: 1) cessation two months before the screening mammogram, 2) cessation one month before, and 3) continued HRT use. We are measuring breast density using a computer assisted method and mammography recall rates from an expert radiologist review of the mammograms; both readers will be blinded to HRT status. We started recruiting women 11/2004; through 5/2005, we have contacted 1119 potentially eligible women. Among women contacted, 30% have agreed, 40% have refused and 30% have been ineligible. Among women who have agreed to participate, 23% have withdrawn from the study. There are several modifications to our study materials that were reviewed and approved by the HSRRB. We have some additional proposed changes to our materials to increase recruitment that will be submitted in June 2005.

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INTRODUCTION:

This randomized controlled trial is designed to test whether short-term (1-2 months) HRT cessation will sufficiently lower breast density to decrease the proportion of women who receive a recommendation for additional evaluation following a screening mammogram, and to examine whether there is a trend by duration of HRT cessation. The study is being conducted at Group Health Cooperative, a managed health care organization with an organized breast cancer screening program. We are using automated to identify HRT users who are due for screening mammograms. Women are being recruited through mailed correspondence and telephone contact. We are projecting that we will recruit between 630-785 women to randomize to one of three HRT arms: 1) cessation two months before the screening mammogram, 2) cessation one month before, and 3) continued HRT use. We are measuring breast density using a computer assisted method. Mammography recall rates are being determined from an expert radiologist review of the mammograms. Both readers are blinded to HRT status. We will test whether: 1) HRT cessation 1 or 2 months before a screening mammogram reduces the likelihood of receiving a recommendation for additional evaluation (recall) compared to women who continue using HRT; 2) HRT cessation for 1 versus 2 months affects the likelihood of receiving a recommendation for additional evaluation; and 3) there is a greater change in breast density (to lower breast density) among women who stop HRT 1 or 2 months before a screening mammogram to those who do not stop HRT. Change in breast density will be measured as the difference between breast density on the screening mammogram before the trial (while on HRT) and during the trial. As part of this trial we will also evaluate: 1) women's tolerance (defined as continued cessation) for short-term (1-2 months) HRT cessation, 2) the rate of HRT re-initiation after participation in the trial, and 3) rates of reported adverse events (return of hot flashes, thromboembolic events within the first 6-months after re-initiation, and return of bleeding with re-initiation among previously amenorrheic women) across randomization groups.

BODY:

Over the past year, we received final study approval from the HSRRB and began recruitment in November 2005 (see below for additional information on IRB process).

Below we outline our progress on the scope of work (SOW) outlined in our original proposal.

Task A. Recruit 1500 women to participate in the trial

We had initially proposed to start recruiting women in the summer of 2003; however, it became clear that the originally proposed recruitment timeline was overly optimistic relative to the IRB review process. In our last annual report, we had expected to start recruiting in August 2004, which was delayed until November 2004, pending final HSRRB approval. Additionally, following the early termination of the estrogen plus progestin arm of the Women's Health Initiative, HRT use has decreased by 40% among members of GHC. Thus, recruitment is substantially behind schedule and the available pool of women has decreased. We are anticipating that we will be able to recruit between 630-785 women for the trial, assuming similar rates of refusal and withdrawal after agreement; these estimates are based on extending recruitment through May 2006. In terms of the tasks in our SOW, we have completed tasks 1-3 (recruitment plan, tracking database, and programs to identify women).

- As of May 31, 2005, we have mailed invitation letters to 1318 women
- Called 1119 to confirm eligibility and invite them to participate
- Contacted physicians that asked to be contacted regarding any of their patients
- Monitored and responded to all calls on our 1-800 number
- Addressed concerns that women have had regarding symptoms.
- To date, we have randomized 244 women: 83 to 1 month cessation; 81 to 2 month cessation and 80 to no cessation.
    - 19 women withdrew after consent and randomization: 7 in the 1 month cessation group; 10 in the 2 month cessation group; and 2 in the no cessation group.

- As of the end of April 2005, 36 women have completed the baseline and follow-up questionnaires and have completed their mammograms; 34 women had mammograms scheduled in May and 56 more in June.

Task B. Develop Study Materials

We have developed all study materials and have received approval for all materials from the local IRB and the HSRRB. We have identified the advocacy board members, have met in person with them twice and have communicated via email.

Task C. Monitor the safety of HRT cessation and initiation

We formed our DSMB when the study began. We met with them for the first time in October 2003, at which point they approved all study materials and the prototype for our DSMB report. It was decided by the DSMB that they would review the study findings three times during the study. We are slated to have our first DSMB meeting with open and closed reports sometime between September and November 2004; approximately 6 months after the first study outcomes become available.

Task D. Study staff read all films for clinical interpretation and breast density measurements for the screening mammograms, blinded with respect to HRT status. Validate HRT cessation/use.

We will be completing the first review of mammograms for density and clinical assessment in June 2005. We have developed the data collection instrument for the clinical assessment form and the tracking database for the mammogram films. We have not yet started monitoring GHC automated pharmacy data for reinitiation, as there has not been sufficient follow-up time to monitor reinitiation. We also incorporated questions into our follow-up questionnaire that ask women to report their intention for restarting HRT and ask women about their compliance with HRT cessation during the study.

Task E. Data quality and control

The data collection instruments we have developed use Teleform technology. What this means is that our instruments are scanned into a computer that has built-in logic checks for the data. As a result, we will not be doing manual data entering of the questionnaires. We will complete the first mammogram readings (for density and clinical assessment) in June 2005. We will be incorporating data quality control measures that include a re-reading of films as we progress with our monthly readings.

Task F. Final analyses and report writing

We have not completed Task F, since both elements require data collection to be completed.

KEY RESEARCH ACCOMPLISHMENTS:

Between June 1, 2004 and May 31, 2005, we have:

- Received final approval from the HSRRB for all recruitment and data collection materials.
- Started recruitment
- Received approval on three IRB modifications from our local IRB and from the HSRRB.
    - Increased the age range of potentially eligible subjects to include women aged 45-49 and 75-79 years.
    - Had an advertisement for our study approved for release in the quarterly GHC North West Health Magazine
    - Added women who have been coming in for mammograms annually, despite their recommended 2 year screening interval by GHC.
- Had a second meeting with our Advocacy Board. They reviewed suggested changes to the recruitment materials and made additional suggestions that we incorporated into our modification request.

Issues we have run into with obtaining IRB approval

We have experience significant delays in start-up by trying to navigate demands from 2 different IRBs, which sometime had conflicting requests in the ways materials should be revised. Additionally, the delay in response time from submissions to HSRRB dramatically impacted our ability to start study recruitment. We have documented the timeline for all submissions to our local IRB and their responses (Appendix A) and have done the same for our submissions to HSRRB and their responses (Appendix B).

Our initial submission to and final approval from GHC and HSRRB is also summarized below.

Brief overview over initial submission and final approval of materials:

To	Content	Submitted	Final approval
GHC	Initial study materials	8/26/04	11/18/03
GHC	Modification #1	11/4/04	12/2/04
GHC	Modification #2	12/1/04	1/3/05
GHC	Modification #3	6/2/04	Pending
HSRRB	Initial study materials	12/5/03	9/21/04
HSRRB	Modification #1	12/10/04	3/28/05
HSRRB	Modification #2	1/10/05	2/16/05

The communications both with our local IRB to comply with HSRRB requests and with HSRRB have consumed an enormous amount of staff time. Additionally, our local IRB has received complaints from the HSRRB about some of the processes that we have in place at GHC. These issues have resulted in GHC's IRB refusal to expedite any additional modification to any study materials in order ensure that there are no further issues or concerns from the HSRRB. This further delays our ability to make changes to any study materials or procedures as we continue recruitment.

REPORTABLE OUTCOMES:

We began recruiting women in November 2004. To date, we have no reportable outcomes.

CONCLUSIONS:

We are experiencing a higher proportion of refusals and withdrawal after agreeing to participate in the trial than is typical for GHC studies. We have spent considerable time talking with our survey department to determine ways we could improve the recruitment materials to address the concerns and/or questions of women who are refusing. We have made modifications to our recruitment materials that address the issues that our survey department has brought up: 1) how will participation directly influence women, and 2) what if women cannot comply with staying off their hormones if they are randomized to one of the 2 cessation arms. Our proposed revisions are being reviewed by the local IRB in June 2005 and we expect to be able to forward documentation of their approval to the HSRRB by the end of June 2005.

One of our key findings to date is that the cohort of women who are still using HRT following the results of the Women's Health Initiative (WHI) may be substantially different than women who were using before WHI. As such, understanding whether this intervention would be acceptable to women still using HRT is likely to become a major focus of this study. For example, if we find that women who stop using hormones have a significant reduction in breast density and/or recall rates, it may be that the intervention is still unacceptable to the majority of women who are still using HRT. We are collecting information on compliance, reinitiation and symptoms, so we will be well positioned to address acceptability of the intervention.

REFERENCES:

N/A

Appendix A: Timeline for Materials Submitted and Received from GHC IRB

Date	*Submitted to*	*Received from*	*Content of submission*
12/6/02	GHC		Original study application without study materials
12/17/02		GHC	Approval in principle the study – clarification of a few procedures and requirement to supply all study materials for review before final approval. The committee granted a waiver of consent to identify subjects for the research project.
7/31/03	GHC		Request for identifying breast cancer survivors from GHC to invite them to participate in our lay advisory board
8/5/03	GHC		Request for approval to change PI from Stephen Taplin to Diana Buist
8/8/03		GHC	Approval of 8/5/03 request for change in PI to Diana Buist
8/14/03		GHC	Expedited approval for 7/31/03 request to form lay advisory board
8/26/03	GHC		Response to 12/17/02 approval in principle Review of study materials: • Informational Letter to all Primary Care Physicians • Letter to Primary Care Phys. for approval of patient(s) • Initial/Recruitment Letter to Subject • Study Brochure • Screening Script • Study Consent Form • HIPAA Consent • Cover Letter to Subject - Consent • Letter To Physicians Informing of Patient Participation • Cover Letter to Subject: Grp 1 – (with Baseline Questionnaire an Study Instr.) • Cover Letter to Subject: Grp 2 – (with Baseline Questionnaire an Study Instr.) • Cover Letter to Subject:Grp 3 – (with Baseline Questionnaire and Study Instr.) • Baseline Questionnaire • Study Instructions Grp1 • Study Instructions Grp2 • Study Instructions Grp3 • Talking points for call from Study Nurse (Stop/Start Instructions) • Cover Letter to Subject (with Follow Up Questionnaire) • Follow-up Questionnaire Grp1&2 • Follow-up Questionnaire Grp 3
9/16/03		GHC IRB	Approval of 8/26/03 materials contingent on modifications to:

Date	*Submitted to*	*Received from*	*Content of submission*
			• Clarification on procedures • Script • Consent form • Invitation letter
10/10/03	GHC		Annual continuation review report
10/13/03	GHC		Response to 9/16/03 approval with modifications (original materials submitted for review 8/26/03): Procedure clarification: Changes to script Consent form Additional changes to documents: • Wording change in MD letter • Brochure • Initial letter to subjects • Screener • Study consent • HIPAA authorization • MD follow-up letter • Cover letter for baseline questionnaire • Baseline questionnaire • Study instructions • Follow-up questionnaire for groups 1 & 2 and group 3
10/21/03		GHC	Review of 10/13/03 investigator's response – additional questions to address: • More specific information on clinical response to symptom management • Clarification of clinical support to women in the study • DSMB draft reports • Consent – continued discussion about wording • Script • Letter
11/11/03	GHC		Submission of revised materials in response to 10/21/03 GHC review. Noted in the application that additional changes were made to the study materials to conform with DOD requirements.
11/14/03	GHC		Submission of revised consent form to replace the consent form submitted to the committee on 11/11/03. The revision was required by a recent change in policy of the HSRRB related to extramural

Date	*Submitted to*	*Received from*	*Content of submission*
			research and medical care for related injuries or illness.
11/18/03		GHC	Approval of materials submitted on 11/11/03 and revised consent on 11/14/03 contingent on: • Nurse and study physician interactions with patients with symptoms • Consent form – ensuring we inform women that they can stay off HT after their mammogram if they want • Script – same comment as the consent above • Survey wording issue
11/18/03		GHC	Continuation report (CRR) approved study through 11/17/04. Noted on the CRR, consent & HIPAA documents currently under review at GHC IRB.
11/25/03	GHC		Modifications to materials as requested from GHC IRB in 11/18/03 memo.
11/25/03		GHC	Approval of revised materials submitted 11/25/03. Original request for modification dated 11/18/03.
4/19/04	GHC		Request wavier of consent for prescreening activities (required by HSRRB) – using automated GHC data to identify potentially eligible women to approach for invitation.
4/21/04		GHC	Approval of waiver of authorization for use of protected health information
8/11/04	GHC		Response to 11/18/03 final approval contingent on finalizing study materials. We previously responded to the 11/18/03 requested changes to the consent form but were unable to submit any other study materials since they were under review at HSRRB. This submission included all study materials that were modified per HSRRB requirements. We also submitted changes to the script and nurse/doctor interactions with patients with symptoms.
8/16/04	GHC		Request for approval of study materials modified per HSRRB requirements. Specific materials include the consent form and HIPAA authorization forms. Due to HSRRB requirements, we separated the consent and HIPAA elements. Also included copies of the protocol approved by HSRRB for information purposes only.
8/25/04		GHC	Approval of consent form submitted 8/16/04 contingent on clarifying eligibility criteria and wording about calling 911.
8/26/04		GHC	Approval of 8/11/04 request for modifications to procedures, script, and survey – approval contingent on removal of a few items: revised materials on hot flashes, changes to risk information to participants and removal of jargon language from study materials.
8/31/04	GHC		Response to 8/26/04 approval of modifications • Changes to READ symptom management • Revised thank you letter and risks and warning signs

Date	*Submitted to*	*Received from*	*Content of submission*
			• Study instruction sheets
8/31/04	GHC		Response to 8/25/04 modification request regarding consent
9/2/04		GHC	Approval of 8/31/04 study materials submitted for modifications
9/2/04		GHC	Approval of 8/31/04 revised consent form
9/8/04		GHC	Documentation of project approval. Documentation that final approval was received by GHC IRB on 11/18/03. All materials for the project as of 9/8/04 have been approved by GHC.
9/16/04	GHC		Annual continuation review
10/19/04		GHC	Approval of project through 10/18/05. Notation that currently approved consent form was not attached but GHC IRB approved the project since they reviewed and approved the consent form in September 2004.
11/4/04	GHC		Request for modification to: • Add study notices to the Center for Health Studies external website and the GHC Northwest Health Magazine • Expand our age criteria to include women aged 45-59 and 75-80 years
11/16/04		GHC	Approval of 11/4/04 study materials contingent on having same study period dates on all study materials.
11/30/04	GHC		Resubmission of study materials with same date in response to 11/16/04 memo from GHC
12/1/04	GHC		Request for modification to: Include women that are self-selecting to come in for mammography every year rather than every 2 years. Changes to materials that would be influenced by the modification request.
12/2/04		GHC	Final approval of 11/30/04 submission for study materials (originally submitted 11/4/04)
12/14/04		GHC	Approval of 12/1/04 request for project modification contingent on revision some wording changes and combing 2 provider letters into 1.
12/22/04		GHC	Additional documentation of level of risk for 11/16/04 modification to satisfy DOD requirement that level of risk be commented on for the approved modification.
12/27/04	GHC		Response to 12/14/04 contingent approval with requested modifications
1/3/05		GHC	Approval of 12/27/04 response from original 12/14/04 request for modification.
3/2/05	GHC		Continuation review completed to satisfy DOD request for clarification surrounding dates of approval for protocol and consent form.
3/15/05		GHC	Full review approval of continuation review through 10/18/05 to ensure that all study materials expire on the same date.

Date	*Submitted to*	*Received from*	*Content of submission*
6/2/04	GHC		Modification request to make changes to materials in an attempt to increase participation rates: • Invitation letter • Survey script • Study brochure • Sending 2nd consent form to nonresponders • Sending 2nd set of questionnaires to nonresponders • Call women who have not returned consent • Call women to complete baseline or follow-up questionnaire via telephone if have not responded to 2 mailings • Changes to protocol that result from the suggested changes described above

Appendix B: Timeline for Materials Submitted and Received from HSRRB

Date	*Submitted to*	*Received from*	*Content of submission*
12/1/03	HSRRB		Letter from GHC acting chair with 310 form for our study to the Commander of the AMRMC
12/5/03	HSRRB		Submission of study materials for first review by HSRRB
2/6/04		Email from Dr. Kimbark	Heads up on informal concerns that the human use reviewer identified after initial review of materials: • HIPAA form • Clarification on who is responsible for follow-up care for participants • Discussion of removing women off hormones in a cyclical fashion (not 1-2 months before mammogram)
3/16/04	In person meeting at Ft. Detrick to discuss protocol		Meeting with PI, Ms. Duchesneau, Dr. Kimbark, Dr. Kenyon, Ms. Bourne and Dr. Beitins at CDMRP and discussed draft of 1st MFR dated 2/20/04.
3/23/04		HSRRB	Receipt of 1st MFR dated 3/16/04. Clarification regarding: • De-linking procedures • Inclusion of women who are pregnant or who have cognitive disorders • Gathering PHI to pre-screen women • Documentation of approval to use information from GHC's Breast Cancer Screening Questionnaire to identify potentially eligible women • Documentation of study materials that have been approved including study protocol, consent form and supporting documents • Revision of protocol to delete duplicate sections • Changing some language in study materials (study brochure) • Provide CVs for study personnel (aside from Co-Investigators) + DSMB members • Provide conflict of interest forms for study investigators • Revisions to the protocol: o Timing of administering HIPAA and consent forms o Risks to potential participants o Minimizing risks to participants o Clarification about provision of medical care o Assigning a medical monitor • Revisions to the consent: o Summarize inclusion/exclusion criteria

Date	*Submitted to*	*Received from*	*Content of submission*
			o Wording of may and should regarding use of HT o When women will get a copy of the signed consent form o Accessing PHI o Clarification that women do not have to receive additional imaging even if recommended o Providing the additional service of scheduling a mammogram o Concept of confidentiality o Clarification of when study investigator talks to subjects o Why have 2 documents – 1 HIPAA and 1 consent • Addressing measures to minimize risks to study participants
3/24/04	Email to Dr. Beitins and Ms. Duchesneau		Further clarification of various items in MFR.
4/1/04	HSRRB		Point-by-point response to 3/16/04 MFR.
5/19/04		HSRRB	Email from Dr. Beitins requesting additional information for the 5/26/04 HSRRB meeting including Draft of 2nd MFR dated 5/14/04 Clarification regarding: • Dates of approved materials • Non-stamped materials • Extent of waiver of consent to use PHI • Series of revisions to the protocol • Revisions to consent form • Risks to subjects
6/16/04		HSRRB	Receipt of draft minutes and recommendations from 5/26/04 HSRRB meeting listing required modifications: • Duration of medical chart abstraction • Revision to adverse events reporting • Consideration of redefining what is an unanticipated risk or reportable event • Additional revisions to Consent forms • Additional revisions to protocol
6/22/04	Email to Dr. Beitins		Further clarification of draft recommendations from 5/26/04 HSRRB meeting. Email forwarded to Ms. Kline to respond to issues.
6/28/04		Email response to 6/22/04 inquiry c/o Ms. Kline	Response to clarification issues raised in 6/22/04 email communication with Dr. Beitins. Sent via email from Ms. Kline.

Date	*Submitted to*	*Received from*	*Content of submission*
7/1/04		HSRRB	Receipt of final minutes from 5/26/04 HSRRB meeting listing required modifications. Some small additional changes to the draft minutes released on 6/16/04.
7/13/04	HSRRB		Response to recommendations from minutes from the 5/26/04 HSRRB meeting. Included: • Revised protocol • 13 revised documents in response to the required recommendations • 6 new documents prepared in response to required recommendations • Revised questionnaire • Document describing the wording changes to the questionnaires • Talking points for study nurse for women going off HRT.
8/9/04		Phone call with Dr. Beitins	Discussion of additional concerns about the protocol.
8/11/04	HSRRB		Revised materials in response to 8/9/04 phone call with Col Brosch including: • Additional changes to protocol • Revision in wording to response document to 5/26/04 MFR • Additional changes to consent form • HIPAA authorization form • Additional changes to fact sheet • Additional changes to study instructions
9/8/04	HSRRB		Submission of all final study materials approved by local IRB with changes to the materials annotated in the cover memo.
9/8/04	HSRRB c/o Dr. Beitins, Dr. Kimbark; Ms. Bourne		Faxed documentation of all communication between local study team and local IRB along with a description of the approval process with local IRB. Documents included IRB correspondence from 12/6/02-4/19/04
9/21/04		HSRRB	Received final approval memorandum issued by Col Brosch on 9/20/04.
11/23/04	HSRRB		Faxed document that provided documentation of approval for our annual continuation review by GHC.
12/10/04		Email from Dr. Beitins	Dr. Beitins responded to an email directed to Dr. Kimbark from Dr. Buist asking for confirmation on the faxed annual continuation review sent on 11/23/04. Dr. Beitins said that page 2 of the fax was unreadable. She also asked for the complete package that the IRB approved along with the IRB letter of approval.
12/10/04	Email to Dr. Beitins		Email to clarify what had been submitted to HSRRB at this point: the annual continuation review for the project. We also clarified that we were going to be sending a modification to the

Date	Submitted to	Received from	Content of submission
			project that we had received after our continuation review.
12/10/04	HSRRB		Submission of 2 documents detailing local IRB approval of 2 proposed amendments along with corresponding change to the recruitment materials: • Placement of study notices on CHS' external website and in the GHC Northwest Health Magazine. • Expanding the age criteria to include women aged 45-49 and 75-80 years.
12/13/04	HSRRB		Faxed document to provide additional materials to De. Beitins: 1) Face page for CRR approval for 10/19/04 2) Consent form approved 9/04
12/13/04		HSRRB email	Request for a letter from GHC IRB confirming final approval of all the modifications and assurances that the level of risk has not been altered from the modifications.
1/4/05	HSRRB		Submission of addition requested documentation of modifications submitted to HSRRB on 12/10/04 that had already been approved by local IRB. We included a letter regarding the impact on the level of risk and a copy of all modified documents approved by the local IRB.
1/10/05	HSRRB		Modification submitted to expand recruitment to women who self-refer themselves for annual mammography.
2/16/05		HSRRB	Approval of: Continuation review submitted 11/23/05 12/10/05 amendment scheduled for 2/23/05 review Question about consent form expiration and a requested explanation of consent form expiration
2/23/05	HSRRB		Response to 2/16/05 memo from Ms. Duchesneau requesting information on the consent form expiration.
3/8/05		HSRRB	Draft recommendations from 2/23/05 HSRRB meeting. Requested a summary/chronology of IRB approval for the protocol, consent form, and study continuation.
3/11/05		HSRRB	Final minutes from 2/23/05 meeting with no changes to recommendations delivered in 3/8/05 draft minutes.
3/24/05	HSRRB		• Response to 2/23/05 continuing review and modification #1 and #2 • Also provided a letter from Barbara Young, PhD, Manager of Research and Human Subjects at GHC describing what happened with our project's review at the October 19, 2004 continuation review • Provided a copy of approval of our new continuation review from 3/15/05, which was completed in response to HSRRB issues raised about our 10/19/04 review • Provided a summary of GHC reviews of this project from

Date	*Submitted to*	*Received from*	*Content of submission*
			8/25/04-3/15/05
3/28/05		HSRRB	Approval of 12/10/05 amendment (age range).